PAPER

Clinical spectrum of cryoglobulinaemic neuropathy

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Background and objective: Cryoglobulinaemic neuropathy (CN) is probably common, as it is usually related to HCV infection. The aim of this study was to delineate the clinical spectrum of CN in a large series and to investigate the factors influencing its expression.
Methods: Seventy one consecutive patients (12 men, 59 women), diagnosed as having CN on the basis of clinical features of neuropathy, clinical and serological findings of mixed cryoglobulinaemia, and exclusion criteria, were identified during a six year period. All patients underwent clinical examination, and electrophysiological and laboratory investigations.
Results: Results of the patients with ''pure'' CN (n = 54) and those with comorbidities (n = 17) were evaluated separately. Of the former 76% had sensory neuropathy (including selective small fibre sensory neuropathy (SFSN) in 14 patients), 15% had sensorimotor polyneuropathy, and 9% had mononeuritis multiplex. The pattern of distribution was similar in the patients with comorbidities. In 30/54 patients, CN was the first manifestation of cryoglobulinaemia. Patients with mild cryoglobulinaemic syndrome had sensory neuropathy more frequently than patients with active syndrome ($p<0.001$), in particular SFSN ($p<0.001$). The latter group had more severe features, with significantly more cases of reduced or absent motor ($p = 0.028$) and sensory action potentials ($p<0.001$), and a tendency towards higher Rankin scores ($p = 0.06$).
Conclusions: Sensory neuropathy, often in the form of SFSN, is by far the commonest form of CN. Cryoglobulinaemia should be vigorously investigated in the diagnosis of sensory neuropathy, especially in older women. Activity of the cryoglobulinaemic syndrome is a major factor influencing the clinical expression and severity of CN.

Cryoglobulinaemic neuropathy (CN) is probably the commonest form of vasculitic neuropathy, at least in the Mediterranean countries. This is because it is usually related to hepatitis C virus (HCV) infection, which affects 1.8–4.8% of the general population.[1 2] However it is likely that CN is underdiagnosed, and our knowledge is mainly based on a few series, most of which included small numbers of patients.[3–6] Recently, studies including large series of patients with HCV related neuropathy with or without cryoglobulinaemia, in which nerve and muscle biopsies of many patients were taken, have been reported.[7 8] This may bias the definition of the spectrum of CN, as nerve biopsy based series tend to include patients with severe forms of the disease and exclude patients with mild peripheral nerve involvement.

We analysed a large series of patients with peripheral neuropathy and mixed cryoglobulinaemia to delineate the full spectrum of neuropathy and investigate the relation between cryoglobulinaemia and peripheral neuropathy. We also aimed to consider the impact of other comorbid factors which often coexist with HCV related mixed cryoglobulinaemia, a multisystem disease.

METHODS

Patients

The study included a cohort of 71 consecutive patients with clinically evident CN, examined in our department on their first visit or at follow up during the period 1998–2003. All patients gave consent, and the study was conducted in accordance with the Declaration of Helsinki with approval from the review board of the Department of Neurosciences. The patients were either directly referred by their general practioners for a diagnostic work-up of peripheral neuropathy or referred by the department of internal medicine for suspected peripheral neuropathy in association with mixed cryoglobulinaemia with or without HCV infection. The criteria for inclusion were as follows:

- clinical evidence of polyneuropathy or mononeuritis multiplex as assessed by a neurologist (FG) in our centre
- diagnosis of mixed cryoglobulinaemia defined as a positive result of cryoglobulin search[9 10]—that is, either cryocrit ⩾1% in at least two determinations or cryocrit <1% in the presence of purpura and/or reduced C4.

Blood samples drawn for the cryoglobulin assay were kept at a temperature of 37°C until coagulation was complete, following which they were stored at 4°C for one or more days. The cryoprecipitate was purified and typed by immunofixation,[10] and cryoglobulinaemia was classified according to Brouet *et al*.[9]

We established the causal relation between mixed cryoglobulinaemia and neuropathy mainly by exclusion of other conditions which could have explained the presence of the neuropathy (''pure'' CN) as follows:

- no history of familial neuropathy, neoplasms, nutritional disorder, or toxin exposure
- no relevant findings on the extensive laboratory examinations, which were in keeping with the recommendations for investigation of peripheral neuropathies.[11 12]

The laboratory examination included urinalysis, haemoglobin, white cell count, platelets, erythrocyte sedimentation rate, fasting blood glucose, serum electrolytes, serum protein electrophoresis and immunoelectrophoresis, serum creatinine, liver function tests, thyroid function tests,

Abbreviations: CN, cryoglobulinaemic neuropathy; HCV, hepatitis C virus; LFSN, large fibre sensory neuropathy; RLS, restless legs syndrome; SFSN, small fibre sensory neuropathy

cryoglobulins, antinuclear antibodies, rheumatoid factor, serum vitamin B_{12} and folate levels, carcinoembryonic antigen, α-fetoprotein, and chest *x* ray. Tests for human immunodeficiency virus were done in a only minority of patients selected on the basis of risk factors. Further studies such as abdominal ultrasound or computed tomography and bone marrow biopsy, were undertaken when appropriate.

The subset of patients with coexistent diseases were classified as ''comorbid'' neuropathy if it appeared that cryoglobulinaemia had a major impact on the peripheral nerve damage in these patients—in particular when cryoglobulinaemia and neuropathy preceded the onset of the other cause(s) or when cryoglobulinaemia was preceded by another cause but its occurrence clearly modified the manifestations of the neuropathy. In contrast, 19 patients who were referred for suspected CN were not included because, in these patients, either cryoglobulinaemia was not as relevant as the other causes of neuropathy (diabetes in three patients, Charcot–Marie–Tooth disease in two patients, and vitamin deficiency in two patients) or because their symptoms and signs could not be unequivocally ascribed to the peripheral neuropathy and were more likely due to (poly)radiculopathy (eight patients) or musculoskeletal disorders (four patients).

All patients underwent a clinical interdisciplinary (internist, neurologist (FG)), electrophysiological and serological–immunological assessment. Purpura was graded as follows: 0, absent; 1, dubious (oedema, and other non-specific skin changes); 2, rare (less than one episode/year); 3, recurring (one or more episodes/year for at least three years) with moderate intensity; 4, recurring with severe intensity; 5, continuous–subcontinuous.

Liver disease was graded according to Niederau *et al*[13] with some modifications: 0, normal/steatosis; 1, fibrosis of varying degree; 2, compensated cirrhosis; 3, decompensated/complicated cirrhosis.

Neurological evaluation

We diagnosed polyneuropathy or mononeuritis multiplex on the basis of sensory and/or motor neuropathic symptoms, present bilaterally in the distal lower extremities to a greater extent than in the hands with diffuse involvement of the peripheral nerves, and in the territories of multiple individual nerves in more than one part of the body. Polyneuropathy was classified as sensory, sensorimotor, or mainly motor on the basis of symptoms according to the criteria of Wolfe *et al*[14] and Notermans *et al*[15] for chronic cryptogenic sensory polyneuropathy. Sensory neuropathy was diagnosed when sensory symptoms were present and motor symptoms absent, although allowing for minimal distal weakness or atrophy in the toe and ankle muscles and subclinical motor electrophysiological abnormalities. Patients with sensory neuropathy were further classified according to the types of fibre involved into: large fibre sensory neuropathy (LFSN; if electroneurography showed abnormal sensory sural nerve action potentials) and ''pure'' small fibre sensory neuropathy (SFSN; diagnosed on clinical grounds if only distal ''small fibre'' sensory symptoms[16 17]—reported as prominent—were present). The modified Rankin scale was used to score disability.[18]

After the start of the study, we performed SF testing with quantitative sensory tests[19] and skin biopsy study of epidermal nerve fibre density[20] in a limited number of patients, but this was not part of the study protocol. Four patients underwent nerve biopsy, which was examined using standard methods.[21]

For statistical analysis, we calculated mean values and standard deviations of continuous variables. These were compared using a *t* test. Categorical variables were evaluated with Fisher's exact test. The Mann–Whitney test was used for the analysis of differences in Rankin scores between the subgroups. A p value <0.05 was considered statistically significant.

RESULTS

Demographic data of the 71 patients included in the study are given in table 1; 54 patients had ''pure'' CN whereas 17 patients had comorbidities (diabetes or glucose intolerance (n = 12), alcohol (n = 2), chemotherapeutic drugs (n = 2) and Sjögren's syndrome (n = 1)). The two groups will be considered separately.

Most of the patients in the ''pure'' CN group were women, with onset of neuropathy mainly in the sixth decade, often as a presenting manifestation of cryoglobulinaemia. HCV antibodies were found in 49/54 patients and qualitative HCV-RNA was positive in 39/39 patients tested. The serum levels of liver enzymes were normal or mildly increased (alanine aminotransferase <60 U/l) in most of the patients (35/54). Sensory neuropathy, often asymmetrical, was present in most patients (76%), with features of SFSN in a quarter of patients. Mononeuritis multiplex of the limb nerves was uncommon (table 2) and none of the patients had a mainly motor polyneuropathy. LFSN usually manifested with prominent positive sensory symptoms such as tingling, and symptoms suggesting associated small fibre involvement were often present. Sensory ataxia as the major manifestation was rarely seen. In SFSN, the main symptoms and signs were burning feet, pain, and restless legs syndrome (RLS), but none of the patients complained of symptoms suggesting autonomic dysfunction. In HCV-negative patients, mononeuritis multiplex was significantly more frequent (2/5 *v* 3/49; p = 0.062). There was a trend for patients with a

Table 1 Baseline demographic data of 71 patients with cryoglobulinaemic neuropathy (CN)

Variable	''Pure'' CN (group 1)	''Comorbid'' neuropathy (group 2)	Total	p (1 *v* 2)
Number	54	17	71	
Men/women	9/45	3/14	12/59	NS*
Age (in years) at observation (mean (SD))	63.6 (9.3)	67.3 (11.3)	64.5 (9.8)	NS†
Age (in years) at onset (mean (SD))	57.7 (9.6)	63.4 (11.6)	59.0 (10.3)	NS†
Disease duration in years (mean (SD))	5.9 (5.8)	4.1 (5.3)	5.4 (5.7)	NS†
HCV antibodies + (n (%))	49 (91)	15 (88)	64 (90)	NS*
Onset with polyneuropathy (n (%))	30 (56)	3 (18)	33 (46)	0.011*
Onset with purpura (n (%))	42 (78)	9 (22)	51 (72)	NS*
Rankin score (1/2/3/4)	16/29/8/1	3/10/4/0	19/39/12/1	NS‡
Purpura grading (0/1/2/3/4/5)	6/9/11/16/10/2	2/3/6/4/2/0	8/12/17/20/12/2	NS‡
Hepatopathy staging (0/1/2/3)	17/29/5/3	2/8/6/1	19/37/11/4	NS‡

*Fisher's exact test; †*t* test; ‡Mann–Whitney U test.
HCV, hepatitis C virus; NS, not significant.

Table 2 Clinical features of 71 patients with cryoglobulinaemic neuropathy (CN)

Pattern	"Pure" CN (1)	"Comorbid" neuropathy (2)	Total	p (1 *v* 2)*
Number	54	17	71	
Sensory neuropathy (n (%))	41 (76)	11 (65)	52 (73)	NS
Asymmetrical	13 (24)	2 (12)	15 (21)	NS
SFSN	14 (26)	4 (24)	18 (25)	NS
LFSN	27 (50)	7 (41)	34 (48)	NS
Sensorimotor neuropathy (n (%))	8 (15)	5 (29)	13 (18)	NS
Mononeuritis multiplex (n (%))	5 (9)	1 (6)	6 (8)	NS
Symptoms (n (%))				
Tingling	33 (61)	6 (35)	39 (55)	NS
Sensory ataxia	21 (39)	6 (35)	27 (38)	NS
Thermal dysesthesia	24 (44)	6 (35)	30 (42)	NS
Pain	19 (35)	11 (65)	30 (42)	0.048
RLS	27 (50)	5 (29)	32 (45)	NS
Rankin score (1/2/3/4)	16/29/8/1	3/10/4/0	19/39/12/1	NS†
Absent ankle jerks (n (%))	26 (48)	9 (53)	35 (49)	NS
Reduced/absent MAPs (n (%))	28 (52)	7 (41)	35 (49)	NS
Reduced/absent SAPs (n (%))	40 (74)	13 (76)	53 (75)	NS

*Fisher's exact test except †Mann–Whitney U test for differences between Rankin scores.
LFSN, large fiber sensory neuropathy; MAPs, motor action potentials; NS, not significant; RLS, restless legs syndrome; SAPs, sensory action potentials; SFSN, small fiber sensory neuropathy.

shorter duration of neuropathy (less than three years) to have SFSN more frequently (9/26 (35%) *v* 5/28 (18%); p = 0.218).

Patients with "comorbid" CN had similar patterns of neuropathy and other features. However, in these patients, onset with polyneuropathy was significantly less frequent (see table 1) and pain was more common (see table 2).

On analysing correlations between the features of cryoglobulinaemic syndrome and the manifestations of pure CN, it appeared that patients with purpura graded ⩾3 had sensorimotor neuropathy more frequently than the rest (7/27 *v* 1/27; p = 0.050), whereas sensory neuropathy was more frequent in patients with purpura <3 (24/27 *v* 17/27; p = 0.054). Cryocrit was significantly correlated with the pattern of neuropathy: cryocrit ⩽5% was associated with sensory neuropathy (19/20 *v* 22/34; p = 0.013), in particular with SFSN (11/20 *v* 3/34; p = 0.002), whereas cryocrit >5% tended to be associated with mononeuritis multiplex (5/34 *v* 0/20; p = 0.145).

Table 3 Comparison of 54 patients with "pure" cryoglobulinaemic neuropathy

	Cryoglobulinaemic syndrome		
	Active (n = 21)	Mild (n = 33)	p*
Age in years (mean (SD))	64.62 (7.20)	62.91 (10.41)	NS†
Duration in years (mean (SD))	7.56 (5.87)	4.79 (5.6)	NS†
Pattern			
Sensory neuropathy (n (%))	10 (48)	31 (94)	<0.001
Asymmetrical	3 (14)	10 (30)	NS
SFSN	0 (0)	14 (42)	<0.001
LFSN	10 (48)	17 (52)	NS
Sensorimotor neuropathy	7 (33)	1 (3)	0.004
Mononeuritis multiplex	4 (19)	1 (3)	0.069
Symptoms			
Tingling	15 (71)	18 (55)	NS
Sensory ataxia	12 (57)	9 (27)	0.045
Thermal dysesthesia	8 (38)	16 (48)	NS
Pain	8 (38)	11 (33)	NS
RLS	10 (48)	17 (52)	NS
Rankin score (1/2/3/4)	3/12/5/1	13/17/3/0	0.06‡
Absent ankle jerks	13 (62)	13 (39)	NS
Reduced/absent MAPs	15 (71)	13 (39)	0.028
Reduced/absent SAPs	21 (100)	19 (57)	<0.001

*Fisher's exact test, except †*t* test, and ‡Mann–Whitney U test for differences between Rankin scores.
LFSN, large fiber sensory neuropathy; MAPs, motor action potentials; NS, not significant; RLS, restless legs syndrome; SAPs, sensory action potentials; SFSN, small fiber sensory neuropathy.

To analyse further the correlations between cryoglobulinaemic syndrome and the features of neuropathy, we divided the patients with "pure" CN into two subgroups of cryoglobulinaemic syndrome based on purpura and cryocrit (table 3): (*a*) those with active syndrome—that is, with intense recurring purpura (grade ⩾3) and cryocrit >5%, and (*b*) those with mild syndrome—that is, with rare or absent purpura (grade <3) or cryocrit ⩽5%. On comparing the features of neuropathy in the two subgroups we found a strong correlation between the activity of cryoglobulinaemia and pattern and severity of neuropathy. Sensory neuropathy, and in particular SFSN, was significantly more common in the subgroup with mild syndrome, whereas mononeuritis multiplex and sensorimotor neuropathy were almost exclusively associated with active cryoglobulinaemic syndrome. In this subgroup there was evidence of more severe peripheral nerve involvement: a significantly greater number of patients had decreased or absent motor and sensory action potentials, with tendency to higher Rankin scores. No significant correlation was found between hepatopathy score, liver enzymes, and the features of neuropathy.

The quantitative sensory tests results were abnormal in nine of 11 patients with SFSN examined, especially for cold pain (8/11) and cold sensation threshold (6/11). Four patients had paradoxical heat sensation.[22] Intraepidermal nerve fibre density, compared with normative data from literature, was abnormal (<3.8 mm[20]) in 6/9 patients, including 1/2 patients with SFSN.

Sural nerve biopsies were taken from four patients. Of these, two patients (both women) have been previously reported (case 1 and case 2 with epineurial vasculitis with multifocal fibre loss, and thickening of the endoneurial microvessels with large fiber loss, respectively[23]). The other two patients (both men, aged 53 and 41 years), who had alcohol comorbidity, had multifocal fibre loss with perivascular lymphocyte infiltrates, suggesting that cryoglobulinaemia plays a significant role in nerve damage.

DISCUSSION

This study aimed to delineate the clinical spectrum of CN in a large series of patients diagnosed with clinical criteria. Although nerve biopsy is the gold standard for diagnosis of CN,[4] we think that the diagnosis can be determined confidently in most patients using clinical criteria, encompassing

the entire spectrum of CN, including the mild forms of neuropathy. The use of nerve biopsy, which is an invasive procedure, should be restricted to patients with severe and/or progressive forms, who may require aggressive treatment.

In our study the clinical features of patients with or without comorbidity were quite similar. This suggests that cryoglobulinaemia usually has a distinct impact on neuropathic manifestations, even in the presence of concurrent diseases. Our data showed that in most of our cases CN was a sensory neuropathy and only rarely a mononeuritis multiplex. It mainly affected women in the sixth and seventh decades, and it was the initial manifestation of mixed cryoglobulinaemia in about half of the patients, which is in agreement with previous observations.[5] It is of interest that several patients had SFSN because cryoglobulinaemia is not usually listed among the causes of SFSN,[16 17 24] and vasculitis in general is considered a rare cause.[25] Clinical diagnosis of SFSN may be corroborated by laboratory tests, in particular skin biopsy[20] and quantitative sensory tests.[19] However, definite diagnostic criteria for SFSN have not yet been formulated.[16] Therefore in our study design we included only clinical criteria, because diagnostic sensitivity of laboratory tests for SFSN is not absolute[16 17]—that is, normal studies do not exclude SFSN. Nonetheless, in a subset of patients, efficacy of the clinical diagnosis was supported by abnormal findings in the laboratory tests for SFSN.

The reason for preferential involvement of small fibres in certain neuropathies is not clear, but it is possible that microangiopathy, a typical feature of diabetic neuropathy which is often an SFSN,[26] represents a condition that preferentially affects small fibres. Although it has been claimed that ischaemia preferentially involves small fibres,[27] this is controversial, and it seems more likely that selective loss of small and large sensory fibres simply represents the extremes of a continuous distribution, as demonstrated by sural nerve morphometry in diabetic neuropathy.[28 29] In addition, it has been shown in skin biopsy studies that pure LFSN is uncommon and such patients almost invariably have a mixed sensory fibre class sensory neuropathy[30]; indeed, our patients who were conventionally classified as LFSN also had coexisting SF-type symptoms. As SFSN is commoner in patients with milder cryoglobulinaemic syndrome, and with a tendency towards shorter duration of neuropathy, it seems to represent mild and/or early disease, possibly evolving later to LFSN. Besides classic symptoms of small fibre involvement, RLS was also frequently found, supporting the idea that RLS may be an expression of SFSN.[31 32]

In the past few years, it has been suggested that glucose intolerance has a role in many cases of otherwise idiopathic sensory neuropathy, and especially in SFSN,[33 34] although it was contradicted in a recent case–control study.[35] We did not routinely undertake oral glucose tolerance tests in our series. However, most of our patients had a disease course of several years without development of overt diabetes, and thus we do not think that glucose intolerance should be considered as an alternative cause of neuropathy.

It is assumed that the pathogenesis of CN involves nerve ischaemia due to damage of the vasa nervorum,[3–5] but this may not be the only mechanism, possibly including either T cell mediated epineurial vasculitis or humoral mediated microangiopathy.[36] It has been suggested,[5] but not confirmed by others,[7] that mononeuritis multiplex is associated with necrotising vasculitis of medium sized vessels and distal polyneuropathy is associated with small vessel vasculitis. The respective pathogenic roles of HCV and cryoglobulin are not fully understood, however, it seems unlikely that nerve damage is caused directly by HCV infection, as local HCV replication has not been demonstrated.[7] It has been suggested that HCV triggers immune mechanisms that ultimately cause ischaemic nerve damage through vasculitis of the medium sized and/or small sized vessels.[8] Although it has been previously stated that manifestations of CN are similar in HCV-positive and HCV-negative patients,[6] we found more cases of mononeuritis multiplex among HCV-negative patients. However, the relevance of this finding is questionable in view of the small number of patients. It is unclear whether deposition of cryoglobulin plays a direct pathogenic role in damage of the vasa nervorum or whether it simply represents an epiphenomenon of the immune reaction. As we have shown in the present study that the activity of cryoglobulinaemic syndrome has a significant impact on the expression of CN, it is likely that pathogenic mechanisms similar to the ones implicated in cutaneous vasculitis are operating in the vasa nervorum. Therefore effective treatment of the cryoglobulinaemic syndrome may be expected to have a favourable impact on neuropathic manifestations.

Although the prevalence of CN in the general population is not documented,[37] it is likely that it is not uncommon, in view of the prevalence of HCV infection. The latter affects an estimated 3.9 million people in the USA and 175 million people globally,[38] and it is quite often complicated by cryoglobulinaemia.[39] Based on the presumption that CN is a quite common disease, it is likely that its mild expression is underrecognised because usually cryoglobulin is not routinely investigated or it may not be detected due to fluctuating serum levels, or because the blood sample was incorrectly handled, or in the absence of overt skin lesions,[40] or because of normal neurophysiological findings in SFSN. The presence of cryoglobulin should be vigorously investigated, including rheumatoid factor and C4 tests as indirect indicators, in women with sensory neuropathy, especially if this is asymmetrical and is associated with prominent positive small fibre-type symptoms, including RLS. In this respect, it is notable that the age range is similar in cryptogenic sensory neuropathy (mean age 63 years, according to Wolfe *et al*[14]), which is otherwise different in that men are more often affected, asymmetrical distribution is not a feature, and large fibre involvement seems more common.

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